REMARKS

Introductory Comments:

Claims 31-81 were examined in the Office Action dated May 17, 2001 and stand variously rejected under 35 U.S.C. §112, first paragraph and 35 U.S.C. §103(a). These rejections and objections are believed to be overcome in part by the above amendments and are otherwise traversed for the reasons discussed below.

Overview of the Above Amendments:

Claims 31 and 34-63 have been amended in order to recite the subject invention with greater particularity. Specifically, claim 31 has been amended to incorporate the recitations from dependent claims 34 to 47 into a Markush group, as well as to recite 90% identity with the specified sequences. Similarly, claims 48 and 56 have been amended to incorporate the recitations from dependent claims 49 to 55 and 57 to 63, respectively, into a Markush group, as well as to recite 90% identity with the specified sequences. Support for this amendment may be found in the original claims, as well as throughout the specification at, e.g., page 16, lines 25-26. Dependent claims 34-47, 49-55 and 57-63 have also been amended to from remove unnecessary language in order to avoid confusion. Claims 34 to 47 and 57 to 63 have been indicated be fully described and enabled by the specification.

New claims 117-127 have been added and pertain to additional embodiments of the invention. Particularly, new claims 117-120 recite nucleic acids encoded V_H and V_L sequences for recombinant antibodies 1:5, 1:7, 1:11 and L3, respectively. Support for these new claims may be found in the claims as originally filed, as well as throughout the specification at, e.g., page 68, lines 26-35.

New claim 121 pertains to an isolated nucleic acid encoding a recombinant monoclonal antibody with specified CDRs interposed between human FRs. The CDRs are recited in two Markush groups which represent the CDRs for the heavy and light chains of recombinant antibodies 1:5, 1:7, 1:11 and L3. New claims 122-125 pertain to the members of the Markush group recited in claim 121. Support for the sequences recited in can be found in Figures 1A-1D and 2A-2D, where the CDRs for the antibodies are

underlined. Further support for new claims 121-125 may be found at page 7, lines 34-35; page 8, lines 4-6; pages 12-13, bridging paragraph; and page 15, lines 4-15.

New claims 126 and 127 also depend from new claims 120 and 121 and find support, for example, on pages 50 through 54.

Drawings

Submitted herewith are corrected Figures 1 through 4 showing SEQ ID NO: in the appropriate spot.

Rejection of the Claims Under 35 U.S.C. §112, First Paragraph:

Claims 31-33, 48, 56 and 64-81 were rejected under 35 U.S.C. §112, first paragraph, as not adequately described by the specification as filed. In particular, the Office alleges that the written description is not commensurate in scope with the claims. Office Action, page 2. The Examiner notes that SEQ ID NO: 15-27 meet the written description and enablement requirements of 35 U.S.C. 112, first paragraph.

Applicants believe the claims are fully described. In particular, the claims have been amended to specify particular sequences acknowledged to be fully described by the specification. Accordingly, the rejection under 35 U.S.C. §112, first paragraph is believed to be overcome and withdrawal thereof is respectfully requested.

Rejection of the Claims Under 35 U.S.C. §103(a):

Claims 31-81 remain rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,308,750 to Mehta et al. ("Mehta), in view of U.S. Patent No. 5,919,454 to Brechot et al. ("Brechot") and further in view of Wong et al., *J. Invest. Med.* (1995) 43:397A ("Wong"). However, applicants submit that the cited combination does not render the claims obvious.

As previously explained, Mehta relates entirely to murine antibodies to putative E2/NS1 proteins of HCV. There is simply no suggestion in Mehta that human monoclonals to E2 could or should be made. Nor is there any suggestion in this reference regarding any nucleic acid sequences for the murine monoclonal antibodies -- the sequences in Mehta's sequence listing are all peptide sequences (see, Mehta, Example 1

for SEQ ID NOs 1-6, and Example 6 for SEQ ID NOs 7-10). In contrast, Applicants claim nucleic acid molecules. Simply put, Mehta does not disclose or suggest the elements of the pending claims.

Brechot and Wong do not provide what is missing from Mehta. As acknowledged by the Office, Brechot does not teach human monoclonal antibodies to HCV E2 and there is no suggestion of nucleic acid molecules encoding such human antibodies.

Wong is similarly deficient. Indeed, Wong is a brief Abstract addressing only murine monoclonal antibodies to HCV E2. Wong discusses how these antibodies may be involved with blocking HCV penetration into cells (last sentence of the Abstract) but there is simply no teaching or suggestion in Wong concerning human monoclonal antibodies that exhibit immunological binding affinity for an HCV E2 antigen. In the absence of any motivation or suggestion regarding the claimed elements, there is no combination of these references that could result in the claimed invention. Thus, the combination does not render the previous claims obvious.

With respect to newly added claims 117-127, as explained above, these claims all recite recombinant antibodies that include particular CDRs. None of the cited art teaches or suggests any of these CDRs. Accordingly, these claims are also believed to be free of the art. Withdrawal of the rejection under 35 U.S.C. §103(a) is therefore respectfully requested.

CONCLUSION

Applicant respectfully submits that the claims comply with the requirements of 35 U.S.C. §112 and define an invention that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Please direct all further written communications regarding this application to:

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

31. (Twice Amended) An isolated nucleic acid molecule encoding a human Fab molecule, comprising:

a first nucleotide sequence encoding a first polypeptide that is homologous to the binding portion of a **γ1** heavy chain variable region (V_H) of said human Fab molecule where said heavy chain region exhibits immunological binding affinity for a hepatitis C virus (HCV) E2 antigen; and wherein the first nucleotide sequence is selected from the group consisting of the contiguous sequence of depicted in Figure 4A (SEQ ID NO:22) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 4B (SEQ ID NO:23) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 4C (SEQ ID NO:24) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 4D (SEQ ID NO:25) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 4E (SEQ ID NO:19) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 4F (SEQ ID NO:26) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; and the contiguous sequence of depicted in Figure 4G (SEQ ID NO:27) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto and

a second nucleotide sequence encoding a second polypeptide that is homologous to the binding portion of a **κ** light chain variable region (V_L) of said human Fab molecule where said light chain variable region exhibits immunological binding affinity for a hepatitis C virus (HCV) E2 antigen, and wherein the second nucleotide sequence is selected from the group consisting of the contiguous sequence of depicted in Figure 3A (SEQ ID NO:15) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 3B (SEQ ID NO:16) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the

contiguous sequence of depicted in Figure 3C (SEQ ID NO:17) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 3D (SEQ ID NO:18) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 3E (SEQ ID NO:19) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 3F (SEQ ID NO:20) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; and the contiguous sequence of depicted in Figure 3G (SEQ ID NO:21) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto, and wherein said Fab molecules have binding affinity greater than 1×10^7 M^{-1} for HCV E2.

34. (Amended) The nucleic acid molecule of claim 31, wherein the first nucleotide sequence is [encoded by the sequence] depicted in Figure 4A (SEQ ID NO:22).

35. (Amended) The nucleic acid molecule of claim 31, wherein the first nucleotide sequence is [encoded by the sequence] depicted in Figure 4B (SEQ ID NO:23).

36. (Amended) The nucleic acid molecule of claim 31, wherein the first nucleotide sequence is [encoded by the sequence] depicted in Figure 4C (SEQ ID NO:24).

37. (Amended) The nucleic acid molecule of claim 31, wherein the first nucleotide sequence is [encoded by the sequence] depicted in Figure 4D (SEQ ID NO:25).

38. (Amended) The nucleic acid molecule of claim 31, wherein the first nucleotide sequence is [encoded by the sequence] depicted in Figure 4E (SEQ ID NO:19).

39. (Amended) The nucleic acid molecule of claim 31, wherein the first nucleotide sequence is [encoded by the sequence] depicted in Figure 4F (SEQ ID NO:26).

40. (Amended) The nucleic acid molecule of claim 31, wherein the first nucleotide sequence is [encoded by the sequence] depicted in Figure 4G (SEQ ID NO:27).

41. (Amended) The nucleic acid molecule of claim 31, wherein the second nucleotide sequence is [encoded by the sequence] depicted in Figure 3A (SEQ ID NO:15).

42. (Amended) The nucleic acid molecule of claim 31, wherein the second nucleotide sequence is [encoded by the sequence] depicted in Figure 3B (SEQ ID NO:16).

43. (Amended) The nucleic acid molecule of claim 31, wherein the second nucleotide sequence is [encoded by the sequence] depicted in Figure 3C (SEQ ID NO:17).

44. (Amended) The nucleic acid molecule of claim 31, wherein the second nucleotide sequence is [encoded by the sequence] depicted in Figure 3D (SEQ ID NO:18).

45. (Amended) The nucleic acid molecule of claim 31, wherein the second nucleotide sequence is [encoded by the sequence depicted] in Figure 3E (SEQ ID NO:19).

46. (Amended) The nucleic acid molecule of claim 31, wherein the second nucleotide sequence is [encoded by the sequence] depicted in Figure 3F (SEQ ID NO:20).

47. (Amended) The nucleic acid molecule of claim 31, wherein the second nucleotide sequence is [encoded by the sequence] depicted in Figure 3G (SEQ ID NO:21).

48. (Twice Amended) An isolated nucleic acid molecule, comprising a first nucleotide sequence encoding a binding portion of a **γ1** heavy chain variable region (V_H) of a human Fab molecule obtained from a combinatorial library, wherein said Fab molecule exhibits immunological binding affinity greater than 1×10^7 M^{-1} for a hepatitis C virus (HCV) E2 antigen and further wherein the first nucleotide sequence is selected from the group consisting of the contiguous sequence of depicted in Figure 4A (SEQ ID NO:22) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 4B (SEQ ID NO:23) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 4C (SEQ ID NO:24) or a contiguous sequence of nucleotides with at

least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 4D (SEQ ID NO:25) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 4E (SEQ ID NO:19) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 4F (SEQ ID NO:26) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; and the contiguous sequence of depicted in Figure 4G (SEQ ID NO:27) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto.

49. (Amended) The nucleic acid molecule of claim 48, wherein the first nucleotide sequence is [encoded by the sequence] depicted in Figure 4A (SEQ ID NO:22).

50. (Amended) The nucleic acid molecule of claim 48, wherein the first nucleotide sequence is [encoded by the sequence] depicted in Figure 4B (SEQ ID NO:23).

51. (Amended) The nucleic acid molecule of claim 48, wherein the first nucleotide sequence is [encoded by the sequence] depicted in Figure 4C (SEQ ID NO:24).

52. (Amended) The nucleic acid molecule of claim 48, wherein the first nucleotide sequence is [encoded by the sequence] depicted in Figure 4D (SEQ ID NO:25).

53. (Amended) The nucleic acid molecule of claim 48, wherein the first nucleotide sequence is [encoded by the sequence] depicted in Figure 4E (SEQ ID NO:19).

54. (Amended) The nucleic acid molecule of claim 48, wherein the first nucleotide sequence is [encoded by the sequence] depicted in Figure 4F (SEQ ID NO:26).

55. (Amended) The nucleic acid molecule of claim 48, wherein the first nucleotide sequence is [encoded by the sequence] depicted in Figure 4G (SEQ ID NO:27).

56. (Twice Amended) An isolated nucleic acid molecule, comprising a first

nucleotide sequence encoding a binding portion of a κ light chain variable region (V_L) of a human Fab molecule obtained from a combinatorial library, wherein said Fab molecule exhibits immunological binding affinity greater than 1×10^7 M^{-1} for a hepatitis C virus (HCV) E2 antigen and further wherein the first nucleotide sequence is selected from the group consisting of the contiguous sequence of depicted in Figure 3A (SEQ ID NO:15) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 3B (SEQ ID NO:16) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 3C (SEQ ID NO:17) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 3D (SEQ ID NO:18) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 3E (SEQ ID NO:19) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 3F (SEQ ID NO:20) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; and the contiguous sequence of depicted in Figure 3G (SEQ ID NO:21) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto.

57. (Amended) The nucleic acid molecule of claim 56, wherein the second nucleotide sequence [is encoded by the sequence] depicted in Figure 3A (SEQ ID NO:15).

58. (Amended) The nucleic acid molecule of claim 56, wherein the second nucleotide sequence is [encoded by the sequence] depicted in Figure 3B (SEQ ID NO:16).

59. (Amended) The nucleic acid molecule of claim 56, wherein the second nucleotide sequence is [encoded by the sequence] depicted in Figure 3C (SEQ ID NO:17).

60. (Amended) The nucleic acid molecule of claim 56, wherein the second nucleotide sequence is [encoded by the sequence] depicted in Figure 3D (SEQ ID NO:18).

61. (Amended) The nucleic acid molecule of claim 56, wherein the second

nucleotide sequence is [encoded by the sequence] depicted in Figure 3E (SEQ ID NO:19).

62. (Amended) The nucleic acid molecule of claim 56, wherein the second nucleotide sequence is [encoded by the sequence] depicted in Figure 3F (SEQ ID NO:20).

63. (Amended) The nucleic acid molecule of claim 56, wherein the second nucleotide sequence is [encoded by the sequence] depicted in Figure 3G (SEQ ID NO:21).

117. (New) The isolated nucleic acid molecule of claim 31, wherein the human Fab molecule encoded by the first and second nucleotide sequences comprises the contiguous sequence of amino acids depicted in Figure 1A (SEQ ID NO: 1) and the contiguous sequence of amino acids depicted in Figure 2A (SEQ ID NO: 5).

118. (New) The isolated nucleic acid molecule of claim 31, wherein the human Fab molecule encoded by the first and second nucleotide sequences comprises the contiguous sequence of amino acids depicted in Figure 1B (SEQ ID NO: 2) and the contiguous sequence of amino acids depicted in Figure 2B (SEQ ID NO: 6).

119. (New) The isolated nucleic acid molecule of claim 31, wherein the human Fab molecule encoded by the first and second nucleotide sequences comprises the contiguous sequence of amino acids depicted in Figure 1C (SEQ ID NO: 3) and the contiguous sequence of amino acids depicted in Figure 2C (SEQ ID NO: 7).

120. (New) The isolated nucleic acid molecule of claim 31, wherein the human Fab molecule encoded by the first and second nucleotide sequences comprises the contiguous sequence of amino acids depicted in Figure 1D (SEQ ID NO: 4) and the contiguous sequence of amino acids depicted in Figure 2D (SEQ ID NO: 8).

121. (New) An isolated nucleic acid molecule that encodes a recombinant human monoclonal antibody that exhibits immunological binding affinity for a hepatitis C virus (HCV) E2 antigen, wherein the antibody comprises at least one group of three

complementarity determining regions (CDRs) interposed between framework regions (FRs) said FRs derived from a human immunoglobulin, wherein the group of three CDRs is selected from the group consisting of amino acid residue numbers 32-36, 51-71, 104-121 of SEQ ID NO:1; amino acid residue numbers 32-36, 51-67, 100-116 of SEQ ID NO:2; amino acid residue numbers 32-36, 51-67, 100-117 of SEQ ID NO:3; amino acid residue numbers 31-35, 50-66, 99-114 of SEQ ID NO:4; amino acid residue numbers 23-34, 49-56, 89-97 of SEQ ID NO:5; amino acid residue numbers 23-33, 49-55, 88-95 of SEQ ID NO:6; amino acid residue numbers 23-34, 50-56, 89-97 of SEQ ID NO:7; and amino acid residue numbers 23-33, 49-55, 88-96 of SEQ ID NO:8.

122. (New) The isolated nucleic acid molecule of claim 121, wherein the antibody encoded by the nucleic acid molecule comprises a first group of CDRs with amino acid residue numbers 32-36, 51-71, 104-121 of SEQ ID NO:1 interposed between FRs, and a second group of CDRs with amino acid residue numbers 23-34, 49-56, 89-97 of SEQ ID NO:5, interposed between FRs, wherein the first and second groups of CDRs interposed between FRs together form a binding site for an HCV E2 antigen.

123. (New) The isolated nucleic acid molecule of claim 121, wherein the antibody comprises a first group of CDRs with amino acid residue numbers 32-36, 51-67, 100-116 of SEQ ID NO:2 interposed between FRs, and a second group of CDRs with amino acid residue numbers 23-33, 49-55, 88-95 of SEQ ID NO:6, interposed between FRs, wherein the first and second groups of CDRs interposed between FRs together form a binding site for an HCV E2 antigen.

124. (New) The isolated nucleic acid molecule of claim 121, wherein the antibody comprises a first group of CDRs with amino acid residue numbers 32-36, 51-67, 100-117 of SEQ ID NO:3 interposed between FRs, and a second group of CDRs with amino acid residue numbers amino acid residue numbers 23-34, 50-56, 89-97 of SEQ ID NO:7 interposed between FRs, wherein the first and second groups of CDRs interposed between FRs together form a binding site for an HCV E2 antigen.

125. (New) The isolated nucleic acid molecule of claim 121, wherein the antibody comprises a first group of CDRs with amino acid residue numbers amino acid residue numbers 31-35, 50-66, 99-114 of SEQ ID NO:4 interposed between FRs, and a second group of CDRs with amino acid residue numbers 23-33, 49-55, 88-96 of SEQ ID NO:8 interposed between FRs, wherein the first and second groups of CDRs interposed between FRs together form a binding site for an HCV E2 antigen.

126. (New) A method for providing an antibody titer to HCV in a mammalian subject, comprising introducing a therapeutically effective amount of a composition comprising the isolated nucleic acid of claim 120 to said subject.

127. (New) A method for providing an antibody titer to HCV in a mammalian subject, comprising introducing a therapeutically effective amount of a composition comprising the isolated nucleic acid of claim 121 to said subject.

Currently Pending Claims

31. (Twice Amended) An isolated nucleic acid molecule encoding a human Fab molecule, comprising:

a first nucleotide sequence encoding a first polypeptide that is homologous to the binding portion of a **γ1** heavy chain variable region (V_H) of said human Fab molecule where said heavy chain region exhibits immunological binding affinity for a hepatitis C virus (HCV) E2 antigen; and wherein the first nucleotide sequence is selected from the group consisting of the contiguous sequence of depicted in Figure 4A (SEQ ID NO:22) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 4B (SEQ ID NO:23) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 4C (SEQ ID NO:24) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 4D (SEQ ID NO:25) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 4E (SEQ ID NO:19) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 4F (SEQ ID NO:26) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; and the contiguous sequence of depicted in Figure 4G (SEQ ID NO:27) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; and

a second nucleotide sequence encoding a second polypeptide that is homologous to the binding portion of a **κ** light chain variable region (V_L) of said human Fab molecule where said light chain variable region exhibits immunological binding affinity for a hepatitis C virus (HCV) E2 antigen, and wherein the second nucleotide sequence is selected from the group consisting of the contiguous sequence of depicted in Figure 3A (SEQ ID NO:15) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 3B (SEQ ID NO:16) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 3C (SEQ ID NO:17) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of

depicted in Figure 3D (SEQ ID NO:18) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 3E (SEQ ID NO:19) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 3F (SEQ ID NO:20) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; and the contiguous sequence of depicted in Figure 3G (SEQ ID NO:21) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto, and wherein said Fab molecules have binding affinity greater than 1×10^7 M^{-1} for HCV E2.

32. The nucleic acid molecule of claim 31, further comprising:

a third nucleotide sequence encoding a first leader sequence peptide, wherein said third nucleotide sequence is operably linked to the 5' terminus of the first nucleotide sequence and is capable of causing secretion of the encoded heavy chain variable region when the encoded heavy chain variable region and the first leader sequence peptide are expressed; and

a fourth nucleotide sequence encoding a second leader sequence peptide, wherein said fourth nucleotide sequence is operably linked to the 5' terminus of the second nucleotide sequence and is capable of causing secretion of the encoded light chain variable region when the encoded light chain variable region and the second leader sequence peptide are expressed.

33. The nucleic acid molecule of claim 32, wherein the third and fourth nucleotide sequences are selected from the group of leader sequences consisting of *omp* A and *pel*B.

34. (Amended) The nucleic acid molecule of claim 31, wherein the first nucleotide sequence is depicted in Figure 4A (SEQ ID NO:22).

35. (Amended) The nucleic acid molecule of claim 31, wherein the first nucleotide sequence is depicted in Figure 4B (SEQ ID NO:23).

36. (Amended) The nucleic acid molecule of claim 31, wherein the first nucleotide sequence is depicted in Figure 4C (SEQ ID NO:24).

37. (Amended) The nucleic acid molecule of claim 31, wherein the first nucleotide sequence is depicted in Figure 4D (SEQ ID NO:25).

38. (Amended) The nucleic acid molecule of claim 31, wherein the first nucleotide sequence is depicted in Figure 4E (SEQ ID NO:19).

39. (Amended) The nucleic acid molecule of claim 31, wherein the first nucleotide sequence is depicted in Figure 4F (SEQ ID NO:26).

40. (Amended) The nucleic acid molecule of claim 31, wherein the first nucleotide sequence is depicted in Figure 4G (SEQ ID NO:27).

41. (Amended) The nucleic acid molecule of claim 31, wherein the second nucleotide sequence is depicted in Figure 3A (SEQ ID NO:15).

42. (Amended) The nucleic acid molecule of claim 31, wherein the second nucleotide sequence is depicted in Figure 3B (SEQ ID NO:16).

43. (Amended) The nucleic acid molecule of claim 31, wherein the second nucleotide sequence is depicted in Figure 3C (SEQ ID NO:17).

44. (Amended) The nucleic acid molecule of claim 31, wherein the second nucleotide sequence is depicted in Figure 3D (SEQ ID NO:18).

45. (Amended) The nucleic acid molecule of claim 31, wherein the second nucleotide sequence is depicted Figure 3E (SEQ ID NO:19).

46. (Amended) The nucleic acid molecule of claim 31, wherein the second

nucleotide sequence is depicted in Figure 3F (SEQ ID NO:20).

47. (Amended) The nucleic acid molecule of claim 31, wherein the second nucleotide sequence is depicted in Figure 3G (SEQ ID NO:21).

48. (Twice Amended) An isolated nucleic acid molecule, comprising a first nucleotide sequence encoding a binding portion of a **γ1** heavy chain variable region (V_H) of a human Fab molecule obtained from a combinatorial library, wherein said Fab molecule exhibits immunological binding affinity greater than 1×10^7 M^{-1} for a hepatitis C virus (HCV) E2 antigen and further wherein the first nucleotide sequence is selected from the group consisting of the contiguous sequence of depicted in Figure 4A (SEQ ID NO:22) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 4B (SEQ ID NO:23) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 4C (SEQ ID NO:24) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 4D (SEQ ID NO:25) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 4E (SEQ ID NO:19) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 4F (SEQ ID NO:26) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; and the contiguous sequence of depicted in Figure 4G (SEQ ID NO:27) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto.

49. (Amended) The nucleic acid molecule of claim 48, wherein the first nucleotide sequence is depicted in Figure 4A (SEQ ID NO:22).

50. (Amended) The nucleic acid molecule of claim 48, wherein the first nucleotide sequence is depicted in Figure 4B (SEQ ID NO:23).

51. (Amended) The nucleic acid molecule of claim 48, wherein the first

nucleotide sequence is depicted in Figure 4C (SEQ ID NO:24).

52. (Amended) The nucleic acid molecule of claim 48, wherein the first nucleotide sequence is depicted in Figure 4D (SEQ ID NO:25).

53. (Amended) The nucleic acid molecule of claim 48, wherein the first nucleotide sequence is depicted in Figure 4E (SEQ ID NO:19).

54. (Amended) The nucleic acid molecule of claim 48, wherein the first nucleotide sequence is depicted in Figure 4F (SEQ ID NO:26).

55. (Amended) The nucleic acid molecule of claim 48, wherein the first nucleotide sequence is depicted in Figure 4G (SEQ ID NO:27).

56. (Twice Amended) An isolated nucleic acid molecule, comprising a first nucleotide sequence encoding a binding portion of a κ light chain variable region (V_L) of a human Fab molecule obtained from a combinatorial library, wherein said Fab molecule exhibits immunological binding affinity greater than 1×10^7 M^{-1} for a hepatitis C virus (HCV) E2 antigen and further wherein the first nucleotide sequence is selected from the group consisting of the contiguous sequence of depicted in Figure 3A (SEQ ID NO:15) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 3B (SEQ ID NO:16) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 3C (SEQ ID NO:17) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 3D (SEQ ID NO:18) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 3E (SEQ ID NO:19) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; the contiguous sequence of depicted in Figure 3F (SEQ ID NO:20) or a contiguous sequence of nucleotides with at least 90% sequence identity thereto; and the contiguous sequence of depicted in Figure 3G (SEQ ID NO:21) or a contiguous sequence of nucleotides with at

least 90% sequence identity thereto.

57. (Amended) The nucleic acid molecule of claim 56, wherein the second nucleotide sequence depicted in Figure 3A (SEQ ID NO:15).

58. (Amended) The nucleic acid molecule of claim 56, wherein the second nucleotide sequence is depicted in Figure 3B (SEQ ID NO:16).

59. (Amended) The nucleic acid molecule of claim 56, wherein the second nucleotide sequence is depicted in Figure 3C (SEQ ID NO:17).

60. (Amended) The nucleic acid molecule of claim 56, wherein the second nucleotide sequence is depicted in Figure 3D (SEQ ID NO:18).

61. (Amended) The nucleic acid molecule of claim 56, wherein the second nucleotide sequence is depicted in Figure 3E (SEQ ID NO:19).

62. (Amended) The nucleic acid molecule of claim 56, wherein the second nucleotide sequence is depicted in Figure 3F (SEQ ID NO:20).

63. (Amended) The nucleic acid molecule of claim 56, wherein the second nucleotide sequence is depicted in Figure 3G (SEQ ID NO:21).

64. An expression vector, comprising the nucleic acid molecule of claim 31 operably linked to control sequences that direct the transcription of the first and second nucleotide sequences whereby said first and second nucleotide sequences can be transcribed and translated in a host cell.

65. The expression vector of claim 64, wherein the control sequences are capable of directing the transcription of the first and second nucleotide sequences in a prokaryotic host cell.

66. The expression vector of claim 64, wherein the control sequences are capable of directing the transcription of the first and second nucleotide sequences in a eukaryotic host cell.

67. An expression vector, comprising the nucleic acid molecule of claim 48 operably linked to control sequences that direct the transcription of the first nucleotide sequence whereby said first nucleotide sequence can be transcribed and translated in a host cell.

68. The expression vector of claim 67, wherein the control sequences are capable of directing the transcription of the first nucleotide sequence in a prokaryotic host cell.

69. The expression vector of claim 67, wherein the control sequences are capable of directing the transcription of the first nucleotide sequence in a eukaryotic host cell.

70. An expression vector, comprising the nucleic acid molecule of claim 56 operably linked to control sequences that direct the transcription of the first nucleotide sequence whereby said first nucleotide sequence can be transcribed and translated in a host cell.

71. The expression vector of claim 70, wherein the control sequences are capable of directing the transcription of the first nucleotide sequence in a prokaryotic host cell.

72. The expression vector of claim 70, wherein the control sequences are capable of directing the transcription of the first nucleotide sequence in a eukaryotic host cell.

73. A prokaryotic host cell transformed with the expression vector of claim

65.

74. A prokaryotic host cell transformed with the expression vector of claim 68.

75. A prokaryotic host cell transformed with the expression vector of claim 71.

76. A eukaryotic host cell transformed with the expression vector of claim 66.

77. A eukaryotic host cell transformed with the expression vector of claim 68.

78. A eukaryotic host cell transformed with the expression vector of claim 72.

79. A method of producing a recombinant human Fab molecule, comprising:

(a) providing a population of transformed host cells according to claim 76; and

(b) expressing said recombinant Fab molecule from the expression vector.

80. A method of producing a recombinant polypeptide having a binding portion of a γ1 heavy chain variable region (V_H) of a human Fab molecule, comprising:

(a) providing a population of transformed host cells according to claim 77; and

(b) expressing said recombinant polypeptide from the expression vector.

81. A method of producing a recombinant polypeptide having a binding portion of a κ light chain variable region (V_L) of a human Fab molecule, comprising:

(a) providing a population of transformed host cells according to claim 78; and

(b) expressing said recombinant polypeptide from the expression vector.

117. (New) The isolated nucleic acid molecule of claim 31, wherein the human Fab molecule encoded by the first and second nucleotide sequences comprises the contiguous sequence of amino acids depicted in Figure 1A (SEQ ID NO: 1) and the contiguous sequence of amino acids depicted in Figure 2A (SEQ ID NO: 5).

118. (New) The isolated nucleic acid molecule of claim 31, wherein the human Fab molecule encoded by the first and second nucleotide sequences comprises the contiguous sequence of amino acids depicted in Figure 1B (SEQ ID NO: 2) and the contiguous sequence of amino acids depicted in Figure 2B (SEQ ID NO: 6).

119. (New) The isolated nucleic acid molecule of claim 31, wherein the human Fab molecule encoded by the first and second nucleotide sequences comprises the contiguous sequence of amino acids depicted in Figure 1C (SEQ ID NO: 3) and the contiguous sequence of amino acids depicted in Figure 2C (SEQ ID NO: 7).

120. (New) The isolated nucleic acid molecule of claim 31, wherein the human Fab molecule encoded by the first and second nucleotide sequences comprises the contiguous sequence of amino acids depicted in Figure 1D (SEQ ID NO: 4) and the contiguous sequence of amino acids depicted in Figure 2D (SEQ ID NO: 8).

121. (New) An isolated nucleic acid molecule that encodes a recombinant human monoclonal antibody that exhibits immunological binding affinity for a hepatitis C virus (HCV) E2 antigen, wherein the antibody comprises at least one group of three complementarity determining regions (CDRs) interposed between framework regions (FRs) said FRs derived from a human immunoglobulin, wherein the group of three CDRs is selected from the group consisting of amino acid residue numbers 32-36, 51-71, 104-121 of SEQ ID NO:1; amino acid residue numbers 32-36, 51-67, 100-116 of SEQ ID NO:2; amino acid residue numbers 32-36, 51-67, 100-117 of SEQ ID NO:3; amino acid residue numbers 31-35, 50-66, 99-114 of SEQ ID NO:4; amino acid residue numbers 23-34, 49-56, 89-97 of SEQ ID NO:5; amino acid residue numbers 23-33, 49-55, 88-95 of SEQ ID NO:6; amino acid residue numbers 23-34, 50-56, 89-97 of SEQ ID NO:7; and

amino acid residue numbers 23-33, 49-55, 88-96 of SEQ ID NO:8.

122. (New) The isolated nucleic acid molecule of claim 121, wherein the antibody encoded by the nucleic acid molecule comprises a first group of CDRs with amino acid residue numbers 32-36, 51-71, 104-121 of SEQ ID NO:1 interposed between FRs, and a second group of CDRs with amino acid residue numbers 23-34, 49-56, 89-97 of SEQ ID NO:5, interposed between FRs, wherein the first and second groups of CDRs interposed between FRs together form a binding site for an HCV E2 antigen.

123. (New) The isolated nucleic acid molecule of claim 121, wherein the antibody comprises a first group of CDRs with amino acid residue numbers 32-36, 51-67, 100-116 of SEQ ID NO:2 interposed between FRs, and a second group of CDRs with amino acid residue numbers 23-33, 49-55, 88-95 of SEQ ID NO:6, interposed between FRs, wherein the first and second groups of CDRs interposed between FRs together form a binding site for an HCV E2 antigen.

124. (New) The isolated nucleic acid molecule of claim 121, wherein the antibody comprises a first group of CDRs with amino acid residue numbers 32-36, 51-67, 100-117 of SEQ ID NO:3 interposed between FRs, and a second group of CDRs with amino acid residue numbers amino acid residue numbers 23-34, 50-56, 89-97 of SEQ ID NO:7 interposed between FRs, wherein the first and second groups of CDRs interposed between FRs together form a binding site for an HCV E2 antigen.

125. (New) The isolated nucleic acid molecule of claim 121, wherein the antibody comprises a first group of CDRs with amino acid residue numbers amino acid residue numbers 31-35, 50-66, 99-114 of SEQ ID NO:4 interposed between FRs, and a second group of CDRs with amino acid residue numbers 23-33, 49-55, 88-96 of SEQ ID NO:8 interposed between FRs, wherein the first and second groups of CDRs interposed between FRs together form a binding site for an HCV E2 antigen.

126. (New) A method for providing an antibody titer to HCV in a mammalian

subject, comprising introducing a therapeutically effective amount of the composition comprising the isolated nucleic acid of claim 120 to said subject.

127. (New) A method for providing an antibody titer to HCV in a mammalian subject, comprising introducing a therapeutically effective amount of the vaccine composition of claim 121 to said subject.